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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,618	02/06/2004	Thomas W. Dubensky JR.	ANZ-1200-UT	8471

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
05/06/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/773,618	DUBENSKY ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/5/09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21,87,106,108,110-113,118,137,139,141 and 143-147* is/are pending in the application.

4a) Of the above claim(s) *108 and 139* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,21,87,106,110-113,118,137,141 and 143-147* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/5/09&2/5/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted on 2/5/09 is made. Claims 20, 21, 87, 106, 110-113, 118, 137, 141 and 143-147 are currently under examination. Claims 108 and 139 are pending and currently withdrawn.

Claim Rejections - 35 USC § 112-2nd paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 20, 21, 87, 106, 110-113, 118, 137, 141 and 143-147 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 and 21 are vague and confusing because it is unclear what is encompassed by 'one or more genetic mutations in uvrA and uvrB genes inhibiting excision repair of said interstrand crosslinks". It the production of functional uvrA and uvrB protein inhibited, etc.? It is unclear what structure, e.g., what mutation, would cause this modified activity. The claim is vague if the same mutation is made in both genes, etc. The metes and bounds of the invention cannot be understood as the mutation is not readily ascertained from the description in the claim. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are

incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. The specific mutation is a critical limitation and must be included in the claim.

Claim 142 is vague and confusing for the phrase "the bacterial gene expression of the bacterium is substantially unaffected by the interstrand crosslinks" because it is unclear if this in reference to all of the genes expressed by the bacterium, the genes other than uvrA and uvrB or only the genes uvrA and uvrB. Accordingly, clarification and/or amendment is requested.

Claim Rejections - 35 USC § 112-Scope of Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 20, 21, 87, 106, 110-113, 118, 137, 141 and 143-147 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "methods of inducing an immune response to a heterologous antigen in a host comprising administering an effective amount of a vaccine comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrAB gene which has been attenuated by treatement with psoralen S-59 (4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen) and ultraviolet light irradiation wherein the mutant bacterium expresses the heterlologous antigen"; "methods of treating disease caused *by L.monocytogeneis* in a host comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrAB gene which has been attenuated by treatement with

psoralen S-59 (4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen) and ultraviolet light irradiation" and "a method of inducing an immune response to a heterologous antigen in a host comprising administering ,an effective amount of a vaccine comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrABgene which has been attenuated by treatement with psoralen S-59 (4'-(4-amino-2-oxa)butyl-4,5',8-trimethylpsoralen) and ultraviolet light irradiation wherein the mutant bacterium expresses the heterologous antigen" and does not reasonably provide enablement for "A method of *preventing* or treating a disease in a host" as currently recited in claim 20 or "a method of inducing an immune response to an antigen" as currently recited in claim 21.The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are broadly drawn to "A method of preventing or treating a disease in a host (or inducing an immune response to an antigen), comprising administering to the host an effective amount of a vaccine comprising a modified L.monocytogenes bacterium, wherein the bacterium comprises psoralen-induced interstrand croslinks introduced between the strands of genomic CAN double helix, said interstrand crosslinks inhibiting replication of said modified bacterium and wherein the bacterium also has one or more genetic mutations in uvrA and uvrB genes inhibiting excision repair of said interstrand crosslinks".

The instant specification has shown that microbial vaccines could be made exquisitely sensitive to killing by treatment with S-59 psoralen and UVA light. Mutant

strains of Listeria monocytogenes were made unable to repair psoralen-DNA corsslinks by deleting the ultraviolet light resistance uvrAB genes which are required for nucleotide-excision repair. It was shown that Listeria monocytogenes uvrAB mutants were much more sensitive to S-59/UVA light inactivation as compared with the parental Listeria monocytogenes strain having intact DNA repair. These mutant, inactivated Listeria monocytogenes uvrAB mutants maintained their metabolic activity and were able to synthesize and create new protein. As a result, these Psoralen/UVA treated Listeria monocytogenes uvrAB mutants retained full ability to infect dendritic cells, escape from the phagolysosome and program presentation of antigen via the class I pathway. Examples 15 and 16 provide successful treatment results using the vaccines comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted uvrAB gene which has been attenuated by treatement with psoralen S-59 and ultraviolet light. The instant claims are not limited to this scope and do not recite that the uvrAB genes were deleted.

The claims read on any mutation to the uvrA and uvrB genes, and to homologs thereof, that have the effect of decreasing the activity of the gene product. The number of potential mutations that may be made is great. Not only are there numerous substitutions that may be made, but there are also large numbers of insertions and deletions that may be made in the polynucleotide sequence. Although the number of operative embodiments is also likely to be high, the lack of guidance leading to them tends to show that they are not readily identifiable. Thus, the factors of claim breadth, guidance, and quantity of experimentation tend to favor a finding of undue

experimentation. While those participating in the art of the relevant technology (genetic and protein manipulation) are generally highly skilled, the art is also rife with complexity. See also, discussion above in the written description rejection (demonstrating the lack of obviousness as to what mutations may be operable absent guidance). Knowledge of the sequence of protein or polynucleotide alone is not sufficient for those skilled in the art to make any mutation to a molecule and have confidence as to the effects that such a mutation would have. See e.g., Bowie, supra. Although Bowie also points out that information gathered from groups of similar or related proteins often helps in making predictions as to the effects of particular mutations. Bowie, pages 1308-1309. However, while the applicant has provided a few related proteins in the specification, there is no discussion as to the structural relationships among them. Rather, the sequences are set out, and it is left to those in the art to run comparisons to determine what the similarities among them are, and to determine which of them are important and which are not. In short, that applicant has invited others in the art to determine what mutations would achieve the desired affect without providing them any guidance indicating what the potential operable embodiments are.

It is the position of the examiner that the novelty of the instantly claimed invention not only lies in the mutation recited in the claims, but the bacterium must be mutated in a certain way in order to attenuate the bacteria in a functional manner, e.g., psoralen and UVA treatment. The specific mutation(s) of the polynucleotide sequence to accomplish decreased biological activity of the encoded polypeptide and the manner of attenuation, is critical to the invention, e.g, not just the phenotype displayed by the

mutant bacterium. Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation. The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of uvrA and uvrB to target for modifications, in order to produce an attenuated bacterium with the desired phenotype. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Bowie et al was also cited for providing evidence that information gathered from groups of similar or related proteins may not be sufficient to show one skilled in the art where to make mutations in a molecule and to have confidence that the mutations will have the desired result (Bowie, pages 1308-1309). Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the

specification to enable those skilled in the art to practice the claimed invention without undue experimentation.

The claims are also broadly drawn to **prevention** and treatment of ***any*** disease, with dependent claims including cancer, HIV, hepatitis and hepatitis C prevention. The specification has not enabled any HIV, cancer or hepatitis ***prevention*** methods. There is no know HIV vaccine prevention method to date. There is also no know cancer prevention method or vaccine to date. This art area is extremely unpredictable. Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims. The state of the prior art is no known prevention methods for these disease, there is extreme unpredictability in treatment and prevention methods in these infectious disease areas, it would take extreme amounts of guidance and direction and a great quantity of experimentation backed by the presence of working examples to enable this scope of the claims. Accordingly, given the lack of guidance contained in the specification, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Response to Applicants' Arguments:

Applicants argue that modification with psoralen (S59) and UVA was widely known and effective in inactivating a wide variety of bacteria in the prior art at the time the invention was made. This does not demonstrate prevention or treating a disease as is claimed. The claims are drawn to a method of treatment or prevention of *any* disease, including more specifically cancer, HIV, hepatitis and hepatitis C prevention. There is no known method of using a vaccine to prevent HIV and cancer. This would not be a matter of routine experimentation, but akin to discovery. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." The bar is set quite high for claims drawn to methods of ***prevention*** and there are no working examples or supporting data or sufficient guidance in the instant specification to teach prevention of disease, particularly HIV and cancer or any hepatitis antigen which was not previously demonstrated to work as a vaccine.

Applicants argue that evidence that the *Listeria* which have been treated with the UV-activated psoralen are capable of protecting mice against subsequent challenge

with wild-type *Listeria* is provided in the instant specification. This argument has been fully and carefully considered, but is not deemed persuasive since none of the claims are limited to protection against disease caused by *Listeria*. Additionally, the results of efficacy against tumors does not directly correlate to HIV or cancer prevention as encompassed by the broad independent claims and specifically recited in some of the dependent claims.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20, 21, 87, 106, 110-113, 118, 137, 141 and 143-147 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 109-112 and 116-119 of U.S. Patent No. 11/502,836. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims encompass methods of inducing an immune response to an antigen

wherein the method uses any bacterium wherein its genomic DNA has been modified so that interstrand crosslinks are introduced between the strands of genomic DNA double helix, said interstrand crosslinks inhibiting replication of said modified bacterium and wherein the bacterium also has one or more genetic mutations in ***any*** uvr genes inhibiting excision repair of said interstrand crosslinks. These claims encompass the scope of the instant claims as uvrA and uvrB genes are encompassed in the scope of 'any uvr genes'. Co-pending claim 114 recite that the microbe is L.moncytogenes and the genes are uvrA and uvrB genes. Accordingly, since the scope of the instant claims is encompassed by the Genus recited in 10/553,809 the scope of the claims are not patentably distinct.

Status of claims

6. The claims are **not** provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 39 and 40 of copending Application No. **10/773,792** because the claims are drawn to mutants with completely different mutations. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. *However, this rejection may apply if amendments are made to the claims of either application*.

The claims are also not rejected under double-patenting with respect to co-pending application **10/883,599** because that application no longer recites any method claims. If that application rejoins any method claims, a double-patenting rejection may be necessitated because the compositions read on the compositions used in the claimed methods.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

4/30/09